行政院國家科學委員會專題研究計畫　成果報告

利用 D-quinic acid 合成 quercitols 和 azepanes 及其他類似物做為 glycosidases 的抑制劑

計畫類別：個別型計畫
計畫編號：NSC93-2113-M-032-007-
執行期間：93 年 08 月 01 日至 94 年 07 月 31 日
執行單位：淡江大學化學系

計畫主持人：施增廉

計畫參與人員：楊如盈

報告類型：精簡報告

處理方式：本計畫可公開查詢

中　華　民　國 94 年 8 月 8 日

附件一

行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告 □期中進度報告

利用 D-(-)-quinic acid 合成 quercitols 和 azepanes 及其他類似物作為 glycosidases 的抑制劑

計畫類別：■ 個別型計畫　　□ 整合型計畫
計畫編號：NSC 93－2113－M－032－007－
執行期間：93　年　8　月　1　日至　94　　年　7　月　31　日

計畫主持人：施增廉
共同主持人：
計畫參與人員：楊如盈

成果報告類型(依經費核定清單規定繳交)：■精簡報告　□完整報告

本成果報告包括以下應繳交之附件：
□赴國外出差或研習心得報告一份
□赴大陸地區出差或研習心得報告一份
□出席國際學術會議心得報告及發表之論文各一份
□國際合作研究計畫國外研究報告書一份

處理方式：除產學合作研究計畫、提升產業技術及人才培育研究計畫、列管計畫及下列情形者外，得立即公開查詢
□涉及專利或其他智慧財產權，□一年□二年後可公開查詢

執行單位：淡江大學

中　華　民　國　九十四　　年　八　　月　八　　日

前言

本報告已有成果發表於 *Tetrahedron* **2005**, *61*, 1919-1924.。另外，我們也合成一系列 azepanes 分子，並且已經透過生化活性測試得知其中一化合物較文獻對某一酵素的抑制性更佳，我們已撰寫論文並將於近期投稿 ChemBio Chem。

研究目的

一般將環內氧原子置換成氮原子的醣類分子，可視為醣類的衍生物之一，通常稱為 azasugars、iminosugars 或 iminocyclitols。研究指出，這類分子對醣水解酵素具有抑制效果。而天然或合成之抑制醣水解酵素分子，可能深具潛力成為抗 HIV、抗癌及抗糖尿病之藥物，所以成為化學家及生物學家所關注的焦點[1]。

過去幾年當中，大多數的化學家皆著重於研究五、六圓環之 azasugars，而七圓環之 azasugars 則較少被深入探討[2]。但七圓環之 azasugars(或稱為 azepanes)，其在結構上較五或六圓環之 azasugars 更具可易變性(flexibility)，而這類 azepane 分子上之羥基(hydroxyl groups)經由和活性中心之羧基(carboxylate groups)形成氫鍵，使 azepanes 更容易嵌入較小的 DNA 凹槽[2,3]，並模仿酵素切除醣類的構形，讓其呈現類似平面結構；例如可以形成半椅形(half-chair)或類似椅子狀(pseudochair)結構，則能和酵素活性中心作鍵結[4]，而達到抑制效果。

許多化學家熱衷於研究環內含異原子(如氮原子或氧原子等)之親水性(hydrophilic)化合物，因這類化合物具較廣泛的生物活性，且具有選擇性的抑制醣分子水解的過程，即為醣水解酵素(glycosidases)或醣轉移酵素(glycosyltransferases)的抑制劑[12,13]，因此，有潛力可當作 AIDS、癌症與代謝失調症，如糖尿病的藥劑。而這類環內含氮原子的化合物可分為 pyrrolidine、piperidine、indolizidine、pyrrolizidine 及 nortropane alkaloids 形式[14]。

於過去的文獻中，大部分皆研究具 C_2 對稱之 tetrahydroxyl azasugars，但少有探討 trihydroxyl azepanes 的合成。而本實驗室以前之成員以 D-(-)-quinic acid 為起始物，成功的合成出 trihydroxyl piperidine 之衍生物[20]，所以我們同樣利用具有掌性性質之 D-(-)-quinic acid 為起始物，如同 Painter 與 Falshaw 的合成概念[12,19a,b]，在相鄰之 diols 經由順式(圖 12)或反式(圖 13)的保護，然後將分子內的雙鍵氧化並經由 $NaIO_4$ 將 diol 進行氧化切除反應，且利用還原氮化之環合反應，隨後切除保護基，即得到一系列具有立體化學特異性的 (3,4,6)-trihydroxyl azepanes。

研究方法

我們使用市售的 D-(-)-quinic acid 為起始物，分別利用 cyclohexanone 進行順式 diol 的保護[21]與 TMB(2,2,3,3-tetramethoxybutane)進行反式 diol 的保護[22,23]，再利用 LAH 進行還原反應後，使用 $NaIO_4$ 氧化切斷 diol。接著使用 MsCl 與 triethylamine 進行消除反應，再利用 Luche's reduction ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH)反應條件還原酮基，得到化合物 **7**, **16**, **22** 經由不同保護基的作用，並經不同雙氧化的條件，然後引入氮原子。經去保護基，得到一系列 azepane 分子。其代表之流程圖如下面兩圖所示。

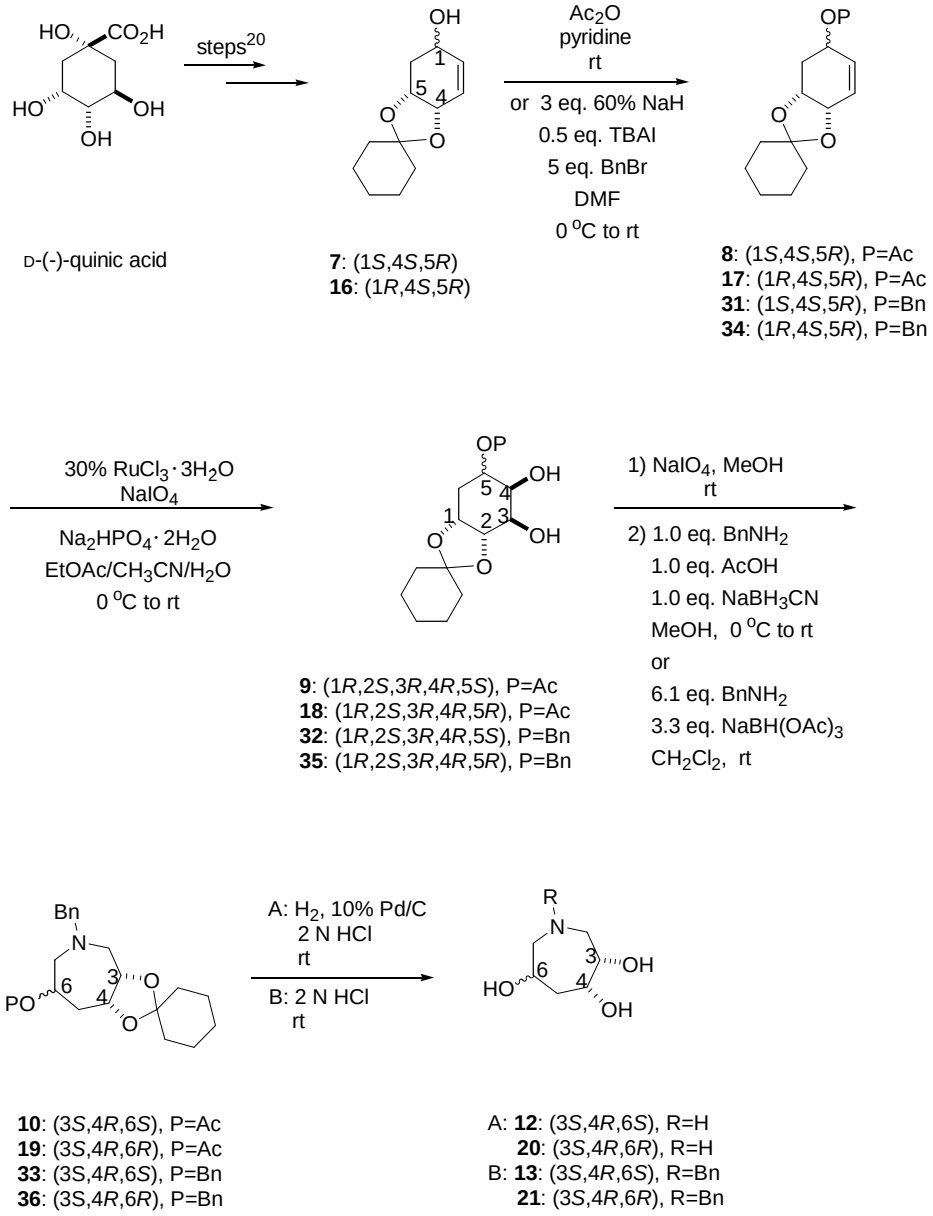


圖 1. 利用 D-(-)-quinic acid 經由 diol 的順式保護，合成一系列(3,4,6)-trihydroxyl azepanes 的流程圖

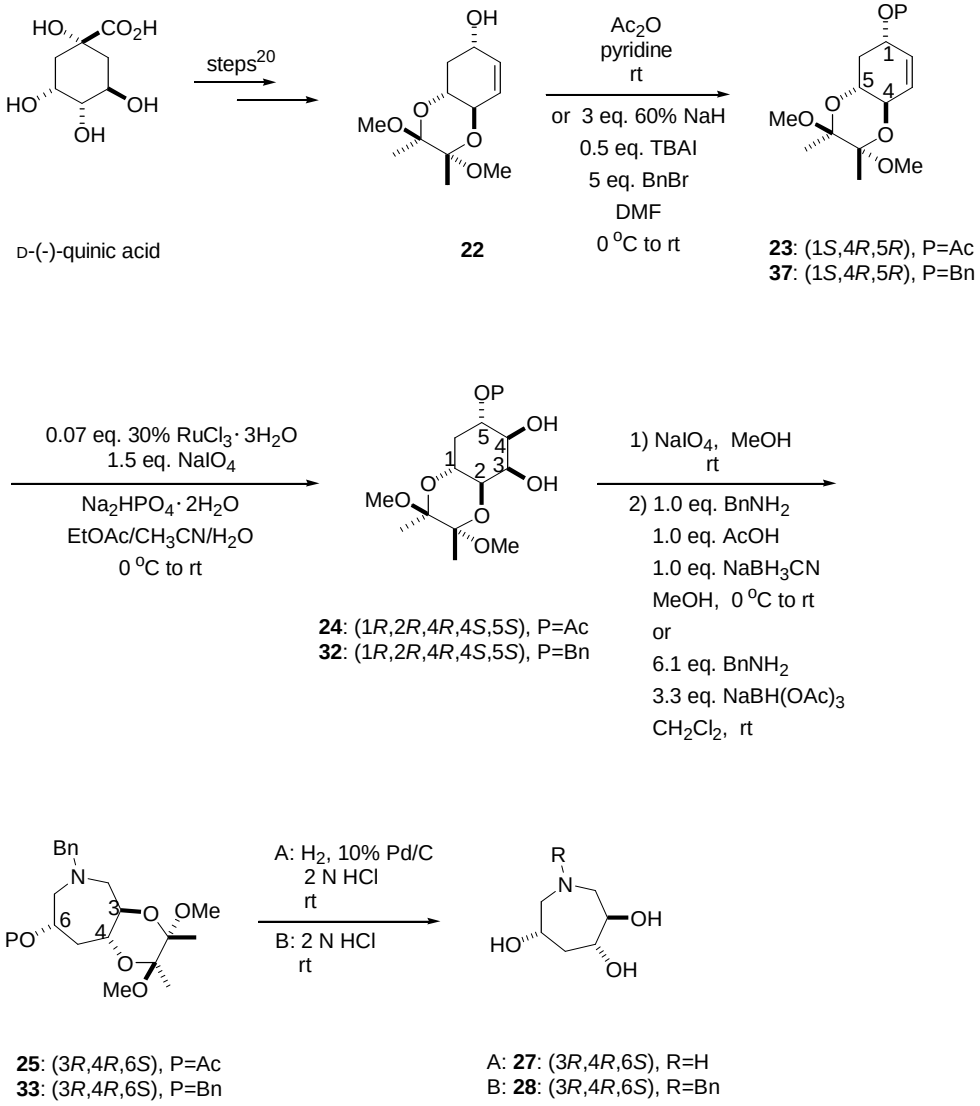
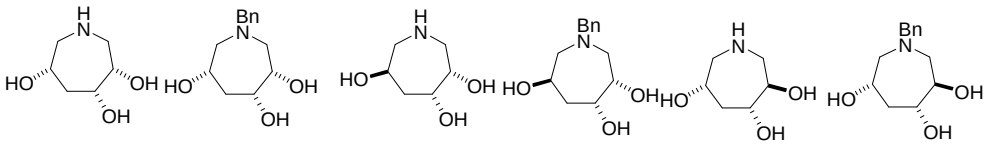


圖 2. 利用 D-(-)-quinic acid 經由反式 TMB 保護 diol，合成一系列(3,4,6)-trihydroxyl azepanes 的流程圖

結果與討論

以上的反應條件讓我們順利得到 **12**,**20**,**27**。在這合成過程中，我們得到一些很重要的訊息；在 dihydroxylation 的條件下，以 $RuCl_3/NaIO_4$ EtOAc:CH_3CN:H_2O = 3:3:1 及加入 buffer 溶液得到較快和較高產率。因為 buffer 溶液防止保護基被切除，所獲得之 dialdehyde 經 reductive amino cyclization 得到 **10**,**19**,**25**,**33**。當保護基為 Ac 時，環合的產率較低；當保護機為 Bn 時，產率可達 70-80%。以上反應之差別在於當 Ac 為保護基時，Ac 會有遷移之現象。另外，最終產物 **12**,**20**,**27** 的光譜圖，由管柱分離後或靜置後一段時間再測得不同。我們懷疑 C-5 位置因非 OH 基，故可靈活調整 7 圓環之構形。以下為生物活性部分，我們將於近期將以上結果分兩部分投稿至國際期刊。



Enzymes	Inhibitor					
α -galatosidase (aspergillus niger)	12.44	10.80	13.24	9.76	20.04	10.06
β -galatosidase (E. coli)	10.55	IC_{50}= 1.26 ㎜±0.13	7.11	IC_{50}= 1.48 ㎜±0.59	2.48	14.55
α -glucosidase (baker yeast)	8.77	11.91	17.44	14.64	33.84	19.48
α -mannosidase (jack bean)	9.44	37.83	8.56	8.22	*K*i=21.14 μ M	8.10
β -mannosidase (sanil acetone)	7.91	37.68	9.32	19.57	11.34	10.82
α -fucosidase (bovine kidney)	11.12	56.19	5.59	35.13	IC_{50}= 0.183 ㎜±0.028	62.52
α -fucosidase (thermotoga maritima maritima)	10.81	IC_{50}= 1.05 ㎜±0.22	24.00	24.64	*K*i=14.85 μ M	IC_{50}= 1.12 ㎜±0.09

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Highly stereoselective and stereospecific syntheses of a variety of quercitols from D-(−)-quinic acid

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Abstract—The highly stereoselective synthesis of (−)-*epi*-, (−)-*allo*- and *neo*-quercitols as well as stereospecific synthesis of (−)-*talo*- and (+)-*gala*-quercitols have been achieved. The general strategy is employing dihydroxylation of the isolated double bond of various kinds of protected chiral (1,4,5)-cyclohex-2-ene-triols, which are derived from D-(−)-quinic acid. The choosing of protecting groups from either BBA (butane 2,3-bisacetal) or acetyl groups will result in the various degrees of stereoselectivity of dihydroxylation. On the other hand, the cyclohexylidene acetal moiety is attributed to the stereospecificity during dihydroxylation to afford the request molecules.

1. Introduction

Quercitol, which is a generic term for cyclohexanepentol or deoxyinositol, has 16 stereoisomers in its family.[1] Among these isomers, there were only (+)-*proto*-, (−)-*proto*- and (−)-*vibo*-quercitols to be found in nature.[2] Due to their biological activities against glycosidases, their syntheses have been attracting a great deal of interest to the synthetic community.[3] At present, ten possible diasteroisomers, *proto*-,[4,5,6] *allo*-,[7,8] *talo*-,[1,2,8,9,10] *epi*-,[1,11] *vibo*-,[12,13,14] *gala*-,[4c,15,16,17] *scyllo*-,[12,18] *neo*-,[1] *cis*-[19] and *muco*-quercitols,[20] have been synthesized from different approaches to provide their either racemic or chiral forms. Recently, we have reported a facile synthesis of (+)-*proto*-quercitol through an important intermediate, (1*R*,4*R*,5*R*)-triacetoxy-cyclohex-2-ene, which was derived from D-(−)-quinic acid.[21] During this course, one key step was employing this intermediate to be dihydroxylated stereospecifically with $KMnO_4/MgSO_4$ condition resulting in moderate yield. This success prompted us that a variety of quercitols might be efficiently synthesized from dihydroxylation of different kinds of protecting chiral (1,4,5)-cyclohex-2-ene-triol analogues. Throughout dihydroxylation, we have found that the protecting groups could affect the outcomes in either stereoselective or stereospecific manners by analysis the resulting quercitols.

Keywords: Quercitol; D-(−)-Quinic acid; Dihydroxylation; Glycosidase.
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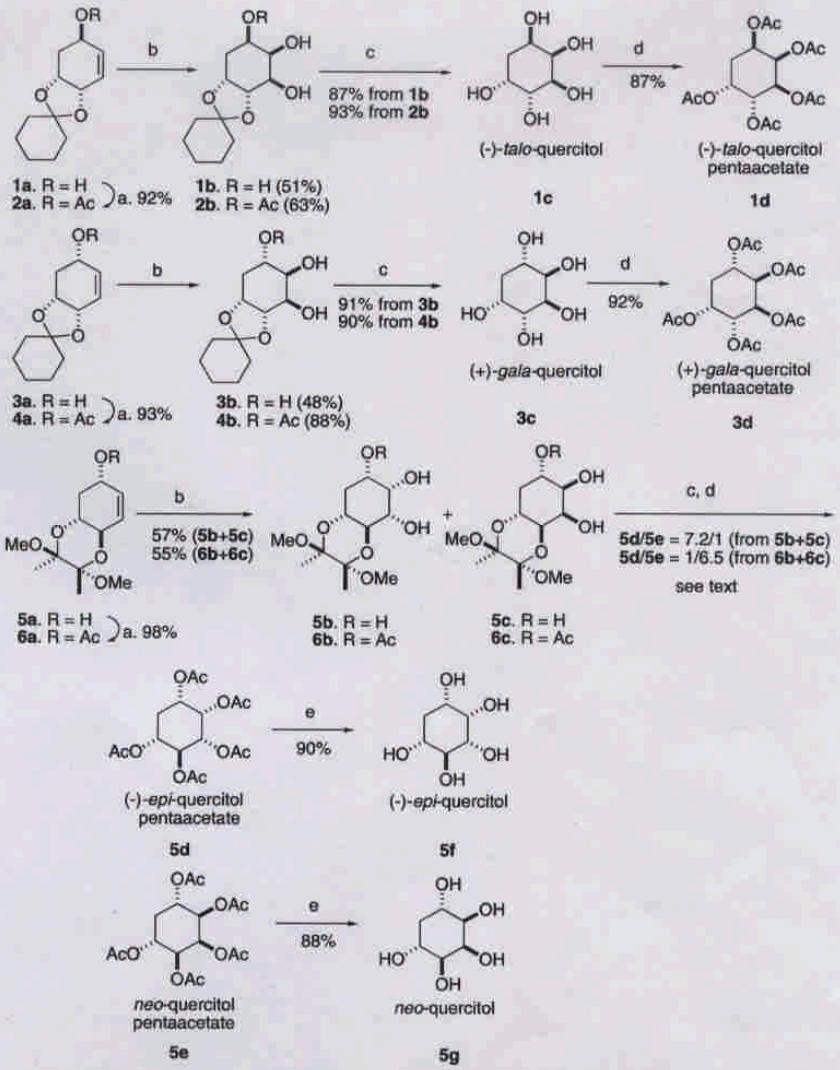
2. Results and discussion

Our synthesis is depicted in Scheme 1 and the results are summarized in Table 1. Compounds **1a**,[21] **3a**[21] and **5a**[22] were acetylated to afford **2a**, **4a** and **6a**, respectively. While **1a** and **2a** were individually dihydroxylated under $KMnO_4/MgSO_4$ condition,[2,4b,4d] the oxidation step gave one product in each case with moderate yield. The resulting stereochemistry of **1b** and **2b** was not determined at this stage. However, the same quercitol **1c** was obtained from either **1b** or **2b** until the removal of their protecting group(s). The spectroscopic data of the resulting quercitol **1c**, (−)-*talo*-quercitol, are in accordance with that of (+)-*talo*-quercitol[10] except the sign of optical rotation. Based on this result, it was obvious that the oxidation proceeded stereospecifically at the same side with the hydroxyl and acetoxy groups but *anti* relationship to the cyclohexylidene acetal group in both cases. Consequently, the same procedure was also employed on compounds **3a** and **4a**. Not surprisingly, the (+)-*gala*-quercitol[23] (**3c**) was received as the sole product. The oxidation happened preferably to the face that was opposite to the stereochemistry of C1 as well as the cyclohexylidene acetal protection of C4 and C5. The stereospecific reactions that occurred in **1a**–**4a** might be explained by the steric effect. The different quercitols will be received if permanganate ion is approaching to the same face with the pseudoaxial oxygen at C4, but that causes the destabilization (Fig. 1). Thus, this factor mainly controlled the stereochemical outcome of dihydroxylation no matter the stereochemistry of C1 with or without protection by acetyl group. Therefore, dihydroxylation occurred at the *anti* relationship to the



Scheme 1. Reagents and conditions: (a) 1.2 equiv Ac_2O, pyridine; (b) 1.5 equiv $KMnO_4$, 1.5 equiv $MgSO_4$, EtOH, H_2O, rt; (c) (i) 80% TFA (for **1b**, **3b**, **5b**, **5c** **6b** and **6c**), (ii) 80% TFA then 7 N NH_3/MeOH (for **2b** and **4b**); (d) excess Ac_2O, pyridine; (e) 7 N NH_3/MeOH.

Table 1. Dihydroxylation of **1a**, **2a**, **3a**, **4a**, **5a** and **6a**

Compound	Yield[a]	Quercitol	$[\alpha]_D$, mp °C (literature)	Quercitol pentaacetate	$[\alpha]_D$, mp °C (literature)
1a/2a	51/63	**1c**	−64.4, 238–248 (+61, 248)[b]	**1d**	−25.4, 184–187 (+28, 183)[b]
3a/4a	48/88	**3c**	+50, 220–230 (−48, 258)[c]	**3d**	+22, an oil (−24, 117)[c]
5a/6a	57/55	**5f**	−3.3, 180–182 (−5, 194)[d]	**5d**	−14.5, an oil (not avilable)
		5g	191–192 (182)[e]	**5e**	237–242 (239)[e]

[a] Yield of dihydroxylation: $KMnO_4$, $MgSO_4$, EtOH, H_2O, rt.
[b] Ref. 1 for (+)-*talo*-quercitol and its pentaacetate.
[c] Ref. 1 for (−)-*gala*-quercitol and its pentaacetate.
[d] Ref. 1 for (−)-*epi*-quercitol and its pentaacetate.
[e] Ref. 1 for *neo*-quercitol and its pentaacetate.

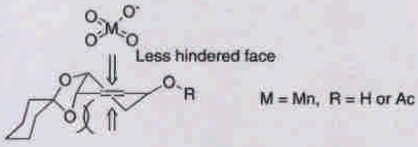


Figure 1. Rationalization of stereospecific dihydroxylation of compounds **1a** and **2a**.

cyclohexylidene acetal moiety and gave the stereospecific oxidation in **1a**, **2a**, **3a** and **4a**. However, we could not eliminate the possibility with respect to the hydroxyl group orienting the dihydroxylation with the assistance of hydrogen bonding in **3a**, but the steric effect deriving from the cyclohexylidene group was somewhat a more determining factor. The above examples were the same as those of Bacli's reports in the syntheses of (±)-*talo*-[2] and (±)-*gala*-quercitols[4c] even though a different protecting group was chosen in our case.

Consequently, compound **5a**[22] was dihydroxylated to give an inseparable mixture of **5b** and **5c**. Thereafter, they were subjected to acetylation and gave the separable compounds **5d** and **5e** with a ratio of 7.2:1 in 87% total yield. Conversely, compound **5e** was isolated as the dominant product when **6a** was dihydroxylated to afford 76% total yield of **5d** and **5e** with a ratio of 1:6.5. Our explanation to these opposite results is indicated in Figure 2. In compounds **5a** and **6a**, the stereo arrangements of BBA group were located at pseudoequatorial positions to accommodate a stable chair form. Therefore, it allowed a less sterically crowded environment than those of previous cases thus contributing equal stereoselectivity to both faces during dihydroxylation. Based on AM1 calculation, the effective distance of ideal intermolecular hydrogen bonding between C1 hydroxyl group with one of closest permanganate's oxygen is 2.17213 Å (Fig. 2a) which is shorter than 2.54892 Å in case of permanganate ion approaching from the opposite site (Fig. 2b). From this point of view, the influence of hydroxyl directing the dihydroxylation through intermolecular hydrogen bonding became the more important factor in **5a**. Consequently, the (−)-*epi*-quercitol (**5f**) was isolated as a major product. On the other hand, the hydroxyl directing effect diminished in **6a** and the permanganate ion was allowed to approach the less sterically hindered face to give the *neo*-quercitol (**5g**) as the main product.

In order to understand where the different kinds of protecting groups affected the outcomes during dihydroxylation, we decided to prepare the triacetates of **7a**, **8a** and **9a** (Scheme 2). It was noteworthy that racemate **8a** has been used in the synthesis of (±)-*gala*-quercitol,[4c] but no study has been shown whereas **7a** and **9a** were conducted under dihydroxylation. We have experienced that moderate yields were obtained from dihydroxylation in $KMnO_4/MgSO_4$ condition in Scheme 1. In order to compare their results, the alternative oxidation using $RuCl_3 \cdot 3H_2O/NaIO_4/H_2SO_4$ condition[24] allowed us to receive the better yields as summarized in Table 2. However, we have found that either stereoselectivity or stereospecificity of **7a** and **9a** decreased dramatically in dihydroxylation except **8a** which gave the (+)-*gala*-quercitol (**3c**) only. The distinction between Scheme 1 and 2 were attributed to both the cyclohexylidene acetal and BBA protecting groups that restricted the more rigid conformations than those of acetyl group upon different chiral (1,4,5)-cyclohex-2-ene-triols. Thus, it is not surprising that the more flexible conformations of **7a** and **9a** gave all less stereoselectivity in dihydroxylation. When compound **7a** was dihydroxylated, an inseparable mixture **7b** and **7c** was obtained. Their separation could be easier after they were acetylated to afford **1d** and **7d** in 39 and 35% yields, respectively. Compound **7d** was subsequently deacetylated to give the (−)-*allo*-quercitol (**7e**).[25] Therefore, the (−)-*talo*- (**1d**) and (−)-*allo*-quercitol pentaacetates (**7d**) were received in almost 1:1 ratio with a 74% combined yield. This observation was distinct from the results of **1a** and **2a** in which the (−)-*talo*-quercitol (**1c**) was the only isolated product (Scheme 1). These opposite results were due to the pseudoequatorial acetyl groups at C1 and C4 of **7a** to contribute equally in stereoselectivity upon dihydroxylation. The (+)-*gala*-quercitol **3c** obtained from **8a** was the same result that appeared in **3a**, **4a** and in Balci's report.[4c] While compound **9a** was dihydroxylated and followed by acetylation, the resulting (−)-*epi*- (**5d**) and *neo*-quercitol pentaacetates (**5e**) were with a 1:1.4 ratio based on ^1H NMR integration. Although the *neo*-quercitol **5g** was slightly dominant in this reaction, however, its stereoselectivity was still far less to that of case of **6a**. The low stereoselectivity was defined the same reason as mentioned in **7a**.

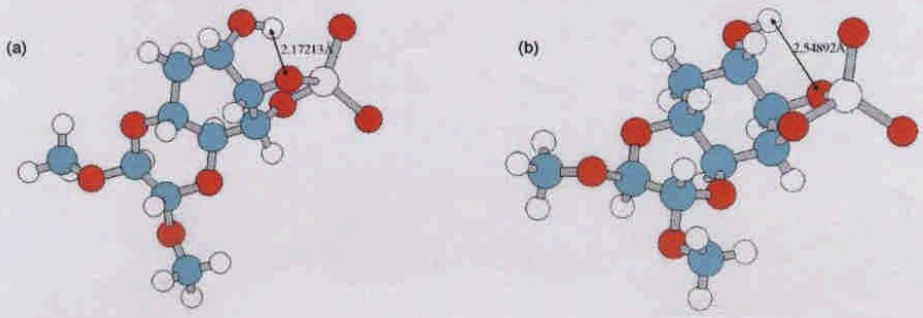
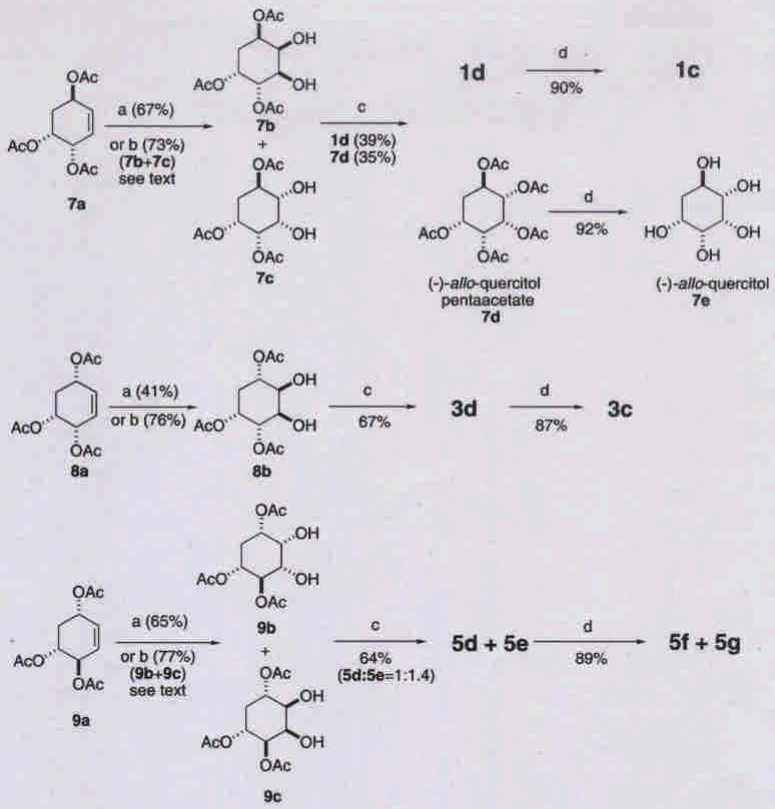


Figure 2. The AM1 calculation of the ideal distance of intermolecular hydrogen bonding in stereoselective dihydroxylation of compound **5a**.



Scheme 2. Reagents and conditions: (a) Method A: 1.5 equiv $KMnO_4$, 1.5 equiv $MgSO_4$, EtOH, H_2O, rt; (b) Method B: $RuCl_3 \cdot 3H_2O$, $NaIO_4$, H_2SO_4, EtOAc, CH_3CN, 0 °C; (c) 5 equiv Ac_2O, pyridine; (d) 7 N NH_3/MeOH.

3. Conclusion

We have successfully synthesized the (−)-*talo*-, (−)-*epi*-, (+)-*gala*-, (−)-*allo*- and *neo*-quercitols from D-(−)-quinic acid with an expedient method. We have learned that the stereoselectivity and stereospecificity of dihydroxylation can be manipulated by choosing the appropriate protecting groups to the analogues of chiral (1,4,5)-cyclohex-2-ene-triols. The stereospecific reaction occurred while cyclohexylidene acetal moiety was used as a protecting group in **1a** and **2a** in which the (−)-*talo*-quercitol was the only isolated product. To the contrary, (−)-*talo*- and (−)-*allo*-quercitols were received with almost equal amounts in **7a** while acetyl groups served as a protecting group. In compounds **5a** and **6a**, the BBA group presented no influence in stereospecificity but their stereoselectivity was controlled by the directing effect of hydroxyl group. Although their degrees of stereoselectivity were moderate,

Table 2. Dihydroxylation of (1,4,5)-triacetoxy-cyclohex-2-enes **7a**, **8a** and **9a**

Compound	Yield[a]/yield[b]	Quercitol pentaacetate (yield)[c]	$[\alpha]_D$, mp °C (literature)	Quercitol (yield)	$[\alpha]_D$, mp °C (literature)
7a	67/73	**1d** (39%)		**1c** (90%)	
		7d (35%)	−15, 103–110 (+11.6, 114)[d]	**7e** (92%)	−23, 237–258 (+23.3, >200)[d]
8a	41/76	**3d** (67%)		**3c** (87%)	
9a	65/77	**5d/5e** (64%) (1:1.4)[e]		**5f/5g**[f] (89%)	

[a] Yield of dihydroxylation; Method A: $KMnO_4$, $MgSO_4$, EtOH, H_2O, rt.
[b] Yield of dihydroxylation; Method B: $RuCl_3 \cdot 3H_2O$, $NaIO_4$, H_2SO_4, EtOAc/CH_3CN (v/v = 1/1).
[c] From Method A.
[d] Ref. 8 for (+)-*allo*-quercitol and its pentaacetate.
[e] The ratio of **5d** versus **5e** was based on the ^1H NMR integration.
[f] The combined yield of **5f** and **5g** were derived from the deacetylation of a mixture of **5d** and **5e**.

however, they were still superior to the results observed in **9a** in which the stereoselectivity dropped tremendously while the acetyl group was used as a protecting group.

4. Experimental

Melting points were recorded on a polarized optical microscopy and equipped with Mettler Toledo FP82HT hot stage and Mettler Toledo FP90 central processor. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-300 MHz. For ^{1}H and ^{13}C NMR spectra, the internal standards were referenced to δ 7.26 and 77.0 ppm, respectively, for $CDCl_3$. While deuterium oxide was used, the internal standard was referenced to 4.69 ppm for ^{1}H NMR and CD_3OD at 49.0 ppm for ^{13}C NMR. The optical rotations were measured on a Horiba Sepa-300 spectrometer. Purification was employed by flash column chromatography using silica gel (230–400 mesh). The purified solid was dissolved in methanol and hexane was added to force the recrystallization occurred.

4.1. General procedures of dihydroxylation

4.1.1. $KMnO_4/MgSO_4$/EtOH condition. All of the reactions were conducted in 0.1–0.2 M. To **1a**, for example, in ethyl alcohol solution at 0 °C was added slowly a mixture of $KMnO_4$ (1.5 equiv) and $MgSO_4$ (1.5 equiv) in distilled water. The reaction was completed within 3–4 h. The resulting mixture was filtrated through celite and the solid was washed with EtOAc and hot water several times. The organic layer was separated, dried with $MgSO_4$ and concentrated. The resulting mixture was purified by flash column chromatography.

4.1.2. $RuCl_3\cdot 3H_2O/NaIO_4/H_2SO_4$ condition. All of the reactions were conducted in 0.1–0.2 M. To an aqueous solution of $NaIO_4$ at 0 °C was added a catalytic amount of concentrated H_2SO_4 and $RuCl_3\cdot 3H_2O$ (5 mol%). To this mixture was slowly added **7a**, for example, in EtOAc/CH_3CN (v/v=1/1). The reaction was completed within 10 min and quenched with $Na_2S_2O_3$ (saturated). The aqueous layer was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$) and concentrated. The resulting mixture was purified by flash column chromatography.

4.1.3. (−)-*talo*-Quercitol [(−)-1-deoxy-*neo*-inositol] (1c).[2] Recrystallization from MeOH and hexane afforded a white solid, 87% yield. $[\alpha]_D^{24}=-64.6$ (*c* 0.5, H_2O); lit.[1] +61, H_2O for (+)-*talo*-quercitol. Mp 238–248 °C; lit.[1] 248 °C. ^{1}H NMR (300 MHz, D_2O): δ 3.82–4.05 (m, 3H), 3.52–3.57 (br s, 2H), 1.78 (dd, J=10.0, 3.2 Hz, 2H). ^{13}C NMR (75.4 MHz, D_2O+CD_3OD): δ 73.7, 71.4, 70.8, 68.8, 66.8, 33.2. HRMS (FAB) calcd for $C_6H_{13}O_5$ (M^++H) 165.0763. Found 165.0754.

4.1.4. (−)-*talo*-Quercitol pentaacetate [(−)-*penta*-*O*-acetyl-1-deoxy-*neo*-inositol] (1d).[2] Purification by flash column chromatography (hexane/EtOAc=5/1) afforded a white solid, 87% yield. $[\alpha]_D^{24}=-25.4$ (*c* 0.3, $CHCl_3$); lit.[1] +28, $CHCl_3$ for (+)-*talo*-quercitol pentaacetate. Mp 184–187 °C; lit.[1] 183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.62 (br s, 1H), 5.52 (dd, J=6.3, 3.3 Hz, 1H), 5.31 (dd, J=10.6, 2.8 Hz, 1H), 5.23 (ddd, J=11.3, 5.1, 2.8 Hz, 1H), 5.20 (dd, J=10.6, 3.3 Hz, 1H), 1.90–2.2 (m+5×CH_3CO, 17H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 170.1, 170.0, 169.9, 169.6, 69.6, 69.0, 67.7, 66.8, 66.1, 28.9, 20.9, 20.7, 20.6, 20.5. HRMS (FAB) calcd for $C_{16}H_{23}O_{10}$ (M^++H) 375.1291. Found 375.1289.

4.1.5. (+)-*gala*-Quercitol [(+)-2-deoxy-*allo*-inositol] (3c).[17b] Recrystallization from MeOH and hexane provided a white solid, 91% yield. $[\alpha]_D^{25}=+50$ (*c* 0.6, H_2O); lit.[16] +50, H_2O. Mp 220–230 °C; lit.[16] 254–255 °C. ^{1}H NMR (300 MHz, D_2O): δ 3.87–3.97 (m, 2H), 3.82 (t, J=3.3 Hz, 1H), 3.70 (ddd, J=11.2, 9.0, 4.5 Hz, 1H), 3.58 (dd, J=9.0, 3.3 Hz, 1H), 1.90 (dt, J=11.6, 4.5 Hz, 1H), 1.62 (dt, J=11.6, 11.2 Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O+CD_3OD): δ 73.1, 72.9, 72.6, 68.8, 67.3, 34.4. HRMS (FAB) calcd for $C_6H_{13}O_5$ (M^++H) 165.0763. Found 165.0758.

4.1.6. (+)-*gala*-Quercitol pentaacetate [(+)-*penta*-*O*-acetyl-2-deoxy-*allo*-inositol] (3d).[4c] Purification by flash column chromatography in gradient (CH_2Cl_2/hexane=1/2–2/1) afforded a pale yellow oil, 92% yield. $[\alpha]_D^{24}=+22$ (*c* 0.5, $CHCl_3$); lit.[1] −24, $CHCl_3$ for (−)-*gala*-quercitol pentaacetate. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (dd, J=5.3, 3.4 Hz, 1H), 5.20–5.30 (m, 3H), 5.11 (ddd, J=13.4, 8.8, 4.6 Hz, 1H), 2.15–2.25 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 1.97–2.06 (m+3×CH_3, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 169.8, 169.4 (×2), 69.8, 68.2, 67.7, 66.7, 29.1, 20.9, 20.8, 20.7. HRMS (FAB) calcd for $C_{16}H_{23}O_{10}$ (M^++H) 375.1291. Found 375.1296.

4.1.7. (−)-*epi*-Quercitol [(−)-2-deoxy-*epi*-inositol] (5f).[10a] Recrystallization from MeOH and hexane gave a white solid, 91% yield. $[\alpha]_D^{25}=-3.3$ (*c* 0.3, H_2O); lit.[1] −5, H_2O. Mp 180–182 °C; lit.[1] 194 °C. ^{1}H NMR (300 MHz, D_2O): δ 3.88 (dd, J=2.9, 1.4 Hz, 1H), 3.60–3.75 (m, 1H), 3.35–3.40 (m, 2H), 3.31 (dd, J=10.2, 2.9 Hz, 1H), 1.82–1.92 (m, 1H), 1.64 (dt, J=11.8, 5.9 Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O+CD_3OD): δ 75.2, 73.8, 72.7, 70.2, 67.4, 34.8.

4.1.8. (−)-*epi*-Quercitol pentaacetate [(−)-*penta*-*O*-acetyl-2-deoxy-*epi*-inositol] (5d). Purification by flash column chromatography (hexane/EtOAc=5/1) afforded a pale yellow oil, 90% yield. $[\alpha]_D^{26}=-14.5$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.50–5.60 (m, 1H), 5.40 (t, J=10.2 Hz, 1H), 4.85–5.10 (m, 3H), 2.20–2.30 (m, 1H), 2.18 (s, 3H), 2.14 (dd, J=7.7, 6.7 Hz, 1H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 170.1, 169.9, 169.8, 169.6, 169.5, 70.7, 69.3, 69.2, 68.7, 66.0, 29.4, 20.8, 20.7, 20.6, 20.5. HRMS (FAB) calcd for $C_{16}H_{23}O_{10}$ (M^++H) 375.1291. Found 375.1291.

4.1.9. *neo*-Quercitol pentaacetate [*penta*-*O*-acetyl-2-deoxy-*neo*-inositol] (5e). Purification by flash column chromatography (hexane/EtOAc=4/1) gave a white solid, 93% yield. Mp 191–192 °C; lit.[1] 182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.59 (t, J=2.9 Hz, 1H), 5.24 (ddd, J=11.5, 10.2, 5.1 Hz, 2H), 5.03 (dd, J=10.2, 2.9 Hz, 2H), 2.52 (dt, J=12.5, 5.1 Hz, 1H), 2.15 (s, 3H), 2.02 (s, 6H), 1.99 (s, 6H), 1.53 (dd, J=12.5, 11.5 Hz, 1H). ^{13}C NMR

(75.4 MHz, $CDCl_3$): δ 169.8, 169.7, 70.8, 68.9, 67.2, 31.6, 20.8, 20.7, 20.5. HRMS (FAB) calcd for $C_{16}H_{23}O_{10}$ (M^+ + H) 375.1291. Found 375.1295.

4.1.10. *neo*-Quercitol [2-deoxy-*neo*-inositol] (5g). Recrystallization from MeOH and hexane gave a white solid, 89% yield. Mp 237–242 °C; lit.[1] 239 °C. ^1H NMR (300 MHz, D_2O): δ 3.94 (t, J=2.8 Hz, 1H), 3.69 (ddd, J=14.4, 11.5, 4.8 Hz, 2H), 3.35 (dd, J=9.7, 2.8 Hz, 2H), 2.08 (dt, J=12.3, 4.8 Hz, 1H), 1.22 (dd, J=12.3, 11.9 Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O+CD_3OD): δ 75.2 (×2), 73.6, 68.4 (×2), 37.7. HRMS (FAB) calcd for $C_6H_{13}O_5$ (M^++H) 165.0763. Found 165.0768.

4.1.11. (−)-*allo*-Quercitol pentaacetate [(−)-*penta*-*O*-acetyl-5-deoxy-*allo*-inositol] (7d).[8] Purification by flash column chromatography in gradient (EtOAc/hexane= 1/10–1/4) gave a white solid, 35% yield. $[\alpha]_D^{24}=-15$ (*c* 0.5, $CHCl_3$); lit.[8] +11.6, $CHCl_3$ for (+)-*allo*-quercitol pentaacetate. Mp 103–110 °C; lit.[8] 114 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 5.38 (t, J=3.4 Hz, 1H), 5.22–5.32 (m, 3H), 5.10 (dd, J=7.0, 3.5 Hz, 1H), 2.27 (ddd, J=14.4, 7.6, 4.0 Hz, 1H), 1.97–2.15 (m, 15H), 1.75–1.89 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 169.8, 169.6, 169.5, 69.0, 68.3, 67.9, 67.2, 66.7, 28.6, 20.9, 20.8, 20.6.

4.1.12. (−)-*allo*-Quercitol [(−)-5-deoxy-*allo*-inositol] (7e).[8] Recrystalization from MeOH and hexane gave a white solid, 96% yield. $[\alpha]_D^{24}=-23$ (*c* 0.4, H_2O); lit.[8] +23.3, H_2O for (+)-*allo*-quercitol. Mp 237–258 °C; lit.[8] 262 °C. ^1H NMR (300 MHz, D_2O): δ 3.93 (ddd, J=13.5, 4.2, 2.5 Hz, 3H), 3.69 (t, J=4.2 Hz, 1H), 3.45 (dd, J=8.1, 3.1 Hz, 1H), 2.02 (ddd, J=14.1, 6.0, 4.6 Hz, 1H), 1.49 (ddd, J=14.1, 9.4, 3.2 Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O+CD_3OD): δ 74.7, 73.3, 71.5, 70.4, 67.3, 34.5.

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